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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,367	03/16/2001	Nobuaki Takahashi	021286/027 8719	6403

7590 09/08/2004

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,367	TAKAHASHI ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39,41-65,71 and 72* is/are pending in the application.

4a) Of the above claim(s) *1-39 and 41-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65 and 71-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 April 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/6/04 has been entered.

2. Claims 1-39, 41-65 and 71-72 are pending.

3. Claims 1-39, and 41-64 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 65 and 71-72, drawn to a method for inhibiting an NK or T cell expressed cell surface MAFA binding to a ligand on target cell using an anti-MAFA antibody, are being acted upon in this Office Action.

5. The specification stands objected to because the "ATCC ___" on page 5 lines 5-9, and page 7, lines 19-23 need to be filled out. The request to this objection be held in abeyance until notification of allowable subject matter is acknowledged.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 65 and 71-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for inhibiting an NK or a T cell expressed cell surface Mast cell function associated antigen (MAFA) binding to a ligand on a target cell in vitro or ex vivo comprising the steps (a) providing an anti-MAFA antibody or an antigen binding fragment thereof that specifically binds to a MAFA polypeptide set forth in any of SEQ ID NO: 1, 3 or 5 wherein antibody binding to the MAFA inhibits the binding of NK or T cell expressed cell surface MAFA to the ligand on the target cell, (b) contacting the anti-MAFA antibody or the

antigen binding fragment thereof that specifically binds to a MAFA on the NK cell or the T cell or the target cell *in vitro* or *ex vivo* in an amount sufficient to inhibit cell surface MAFA binding to its ligand on the target cell, the said method wherein the anti-MAFA antibody or the antigen binding fragment thereof binding to the MAFA expressed on the NK or T cells inhibits the MAFA from generating an inhibitory signal to the NK or the T cell and the said method wherein the anti-MAFA antibody or antibody binding fragment thereof inhibits NK cell or T cell mediated cytotoxicity, **does not** reasonably provide enablement for a method for inhibiting an NK or a T cell expressed cell surface MAFA binding to a ligand on a target cell comprising providing *any* "agonist anti-MAFA antibody or *any* antigen binding subsequence of *any* agonist anti-MAFA antibody" as set forth in claim 65, *any* agonist anti-MAFA antibody generates an inhibitory signal to the NK or the T cells that inhibits any activity (claim 71) such as secretion of any cytokine (claim 72) of the NK or T cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only MAFA from human, rat and mouse comprising SEQ ID NO: 1, 3 and 5, respectively. The specification discloses that antibody and the binding fragment thereof that binds to the extra-cellular domain of mouse MAFA on T cells or NK cells **inhibits** the cytotoxic activity of NK cells or T cells (page 29, and 31). The specification further discloses a method for enhancing the cytotoxic activity of NK cell using recombinant soluble MAFA (Fig 2, page 30).

The specification does not provide sufficient guidance as how to make any "*agonist* anti-MAFA" or *any* antigen binding subsequence of *any* agonist anti-MAFA antibody for the claimed method without the chemical structure of the immunogen (the specific amino acid sequence of immunogen used by Applicants to make any *agonist* anti-MAFA antibody). There is insufficient

guidance as to the immunogen without the amino acid sequence used by applicant to make an *agonist* antibody that would generate an "inhibitory signal" to the NK or the T cell that inhibit all activity such as NK cell or T cell mediated cytotoxicity or NK cell or T cell mediated secretion of which cytokine. There is insufficient guidance as to which antibody binding *subsequence* of which agonist anti-MAFA without the amino acid sequence that would generate an inhibitory signal to the NK or the T cell that inhibit all activity such as NK cell or T cell mediated cytotoxicity or NK cell or T cell mediated secretion of which cytokine.

Kuby *et al*, of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues, it is unpredictable to determine which undisclosed subsequence of *any* anti-MAFA antibody wherein the subsequence "comprises" an antigen binding site would have the same antibody specificity as an antibody generated from the full-length polypeptide.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Abaza *et al*, of record, teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

The specification on page 4 lines 6-11 discloses anti-MAFA antibody or the binding fragment thereof that binds to NK or a T cell expressed cell surface MAFA wherein the antibody binding to the NK or T cell expressed cell surface MAFA inhibits the MAFA from generating an inhibitory signal to the NK or the T cells. Further, there is insufficient working examples demonstrating that all undisclosed agonist antibody and antibody binding *subsequence* of which agonist anti-MAFA would generate an inhibitory signal to the NK or the T cell that inhibit all activity such as NK cell or T cell mediated cytotoxicity or NK cell or T cell mediated secretion of which cytokine for the claimed method.

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/6/04 have been fully considered but are not found persuasive.

Applicants' position is that amended claims 65, 71 and 72 recite that "the agonist anti-MAFA antibody or antigen binding subsequence of the agonist anti-MAFA antibody binds to a MAFA polypeptide set forth in any of SEQ ID NO: 1, 3 or 5. Given the guidance in the specification and knowledge in the art one skilled in the art could practice claims 65, 71 and 72 without undue experimentation.

However, it is noted that the claimed method requires agonist anti-MAFA antibody or any antigen binding subsequence an agonist anti-MAFA antibody. The specification discloses only MAFA from human, rat and mouse comprising SEQ ID NO: 1, 3 and 5, respectively. The specification discloses that antibody and the binding fragment thereof that binds to the extra-cellular domain of mouse MAFA on T cells or NK cells **inhibits** the cytotoxic activity of NK cells or T cells (page 29, and 31). The specification further discloses a method for enhancing the cytotoxic activity of NK cell using recombinant soluble MAFA (Fig 2, page 30).

The specification does not provide sufficient guidance as how to make any "*agonist* anti-MAFA" or *any* antigen binding subsequence of *any* agonist anti-MAFA antibody for the claimed method without the chemical structure of the immunogen (the specific amino acid sequence of immunogen used by Applicants to make any *agonist* anti-MAFA antibody). There is insufficient guidance as to immunizing an animal with which particular immunogen without the amino acid sequence would generate an antibody which agonist activity, let alone the antibody in the claimed method generates an "inhibitory signal" to NK and T cells. The specification on page 4 lines 6-11 discloses anti-MAFA antibody or the binding fragment thereof that binds to NK or a T cell expressed cell surface MAFA wherein the antibody binding to the NK or T cell expressed cell surface MAFA inhibits the MAFA from generating an inhibitory signal to the NK or the T cells.

With regard to an antigen binding subsequence of agonist anti-MAFA antibody, in addition to the problem of making anti-MAFA antibody with agonist activity, the antigen binding

subsequence could be from any undisclosed agonist anti-MAFA for the claimed method. Note, amendment to the claims as suggested below would overcome the enablement rejection since the specification teaches a method of inhibiting NK cell or T cell mediated cytotoxic activity using the specific anti-MAFA or the antigen binding fragment thereof that binds to SEQ ID NO: 1, 3 or 5.

8. Claim 72 is rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The "method...activity inhibited comprises *NK cell or T cell mediated secretion of a cytokine*" in Claim 72 represents a departure from the specification and the claims as originally filed.

It would be helpful if Applicant points out the support for anti-MAFA antibody inhibits NK cell or T cell mediated secretion of cytokine comes from.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 65 and 71-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "an antigen binding subsequence of *an* agonist anti-MAFA antibody" in claims 65, line 3, is ambiguous and indefinite; one of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. It is suggested that the claim 65 be amended to recite "A method for inhibiting an NK or a T cell expressed cell surface Mast cell function associated antigen (MAFA) binding to a ligand on a target cell in vitro or ex vivo comprising the steps (a) providing an anti-MAFA antibody or an antigen binding fragment thereof that specifically binds to a MAFA polypeptide set forth in any of SEQ ID NO: 1, 3 or 5 wherein antibody binding to the MAFA inhibits the binding of NK or T cell expressed cell surface MAFA to the ligand on the target cell, (b) contacting the anti-MAFA antibody or the antigen binding fragment thereof that

specifically binds to a MAFA on the NK cell or the T cell or the target cell *in vitro* or *ex vivo* in an amount sufficient to inhibit cell surface MAFA binding to its ligand on the target cell".

The method "wherein the *agonist* anti-MAFA antibody or the antigen binding subsequence of the agonist anti-MAFA *antibody generates an inhibitory signal* to the NK or the T cell that inhibits an activity of the NK or the T cell" in claim 71 is ambiguous and contradictory. The specification on page 4 lines 6-11 discloses anti-MAFA antibody or the binding fragment thereof binds to NK or a T cell expressed cell surface MAFA wherein the antibody binding to the NK or T cell expressed cell surface MAFA inhibits the MAFA from generating an inhibitory signal to the NK or the T cells. The agonist antibody does not generate an inhibitory signal to the NK or the T cells as claimed. It is suggested that claim 71 be amended to recite "The method of claim 65 wherein the anti-MAFA antibody or the antigen binding fragment thereof binding to the MAFA expressed on the NK or T cells inhibits the MAFA from generating an inhibitory signal to the NK or the T cell".

The method of claim 72 wherein "the activity inhibited comprises NK cell or T cell-mediated cytotoxicity or secretion of a cytokine is ambiguous and indefinite. It is suggested that claim 72 be amended to recite "The method of claim 71 wherein the anti-MAFA antibody or the antigen binding fragment thereof inhibits the activity of NK cell or T cell mediated cytotoxicity.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

13. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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